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Synthesis of New Nucleoside Analogues From 3,5-Disubstituted Pyrazoline

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Abstract

In this work, a series of new nucleoside analogues (β-glucose liked to pyrazoline moiety) was synthesized. In the beginning, chalcone [1-3] was formed from the reaction of acetophenone and benzaldehyde derivatives in the presence of sodium hydroxide. Pyrazolines [4-6] were obtained from the reaction of the prepared chalcones and hydrazine hydrate in the presence of ethanol absolute. These pyrazolines were treated with β-glucose pentaacetate to afford a series of desirable protected nucleoside analogues [8-10]. After that hydrolysis of protected nuclioside analogues in sodium methoxide gave free nucleoside analogues [11-13]. These new formed compounds were diagnosed by 13C-NMR and 1H-NMR for some of them and FT-IR spectroscopy.

Keyword: chalcone , pyrazoline, nucleoside analogues, hydrazine hydrate, β-glucose pentaacetate.

1.INTRODUCTION

1,3-Diaryl-2-propen-1-ones commonly named as chalcones usually occurring α,β-unsaturated ketones with two aromatic rings (A and B) belonging to the flavonoid family [(1)]. These compounds are colored because of the existence of the chromophore -CO-CH=CH-. . There are different ways to prepared chalcones [(2)] .Mostly favorable method is the Claisen-Schimdt condensation of equimolar quantities of arylmethyl ketone with aryl aldehyde in the presence of alcoholic alkali. Chalcones used in the preparation of several compounds such as pyrimidines, cyanopyridines, isoxazoles and pyrazolines having a system of the rings heterogeneous [(3)]. A variety of chalcones have been reviewed for their mutagenic, cytotoxic, chemoprevention agents, anticancer, antiviral, enzyme inhibitory and insecticidal Properties [(4-5)]. Pyrazolines compounds contain five membered heterogeneous which has attracted the attentions of organic chemists in the past decades due to their immense biological applications. These compounds are usually formed from the reactions of chalcones with hydrazine derivatives. [(6)] Pyrazoline derivatives are used as the anticancer, fungicidal, bacteriostatic[(7)], anticonvulsant, analgesics, antifungal, anthelmintic, antipyretic, anti-inflammatory, cardiovascular, selective COX-2 and antimicrobial inhibitory activities [(8)]. One of the compounds that used in the preparation of many medical and pharmaceutical compounds is Nucleoside analogues which are used as therapeutic agent for many diseases caused by antimicrobial agents, HIV, anticancer agents and hepatitis. [(9)] .

2.MATERIAL AND METHOD

All chemicals used were supplied by: Merck, BDH, Fluka and sigma Aldrich chemical companies.

Preparation of chalcones [1-3] [(10)]

A mixture of acetophenone (0.025 mole) and benzaldehyde derivatives (0.025 mole) was dissolved in ethanol (8 ml), then NaOH 30% (4 ml) was added dropewise. The mixture was stirred in ice cold water bath until it solidified. Then the solidified mass is kept in cold condition overnight and after that solidified mass separated and dried at room temperature to give compounds.

FTIR and physical properties of chalcones [1-3] were mentioned in Table (1).

Synthesis of pyrazoline [4-6] [(11)]

A mixture of chalcone (0.01 mole) and hydrazine hydrate (0.01 mole) was dissolved in absolute ethanol (10 ml) and refluxed for 9-10 hours then poured into crushed ice and stirred. The solid was obtained, filtered off and washed with water and dried. The FTIR and physical properties of pyrazolines [4-6] were mentioned in Table (2).

Synthesis of β-glucose penta acetate [7] [(12)]

B-Glucose (0.005 mole) and (0.0097 mole) of anhydrous sodium acetate were dissolved in 6 ml acetic anhydride then refluxed on water bath with stirring for (2 hour). After that, the mixture was poured into 50 ml of ice-cold water , filtered and recrystallized from ethanol . FTIR and physical properties of compound [7] was mentioned in Table (3).

Synthesis of nucleoside analogues [8-10] [(13)]

(0.0108 mole of β-glucose penta acetate was dissolved in 10 ml dry benzene , then (0.0005 mole) of pyrazoline derivatives [4-6] were added and refluxed with vigorous stirring for one hour. The resulted mixture was cooled to room temperature, then filtered and washed with 5 ml ethanol, then dried to give protected nucleosides [8-10]. FTIR and physical properties of compounds [8-10] were mentioned in Table (3).

Hydrolysis of nucleoside analogues [11-13] [(14)]

A solution of the blocked neocleoside (0.15 gm) in 7 ml of methanolic sodium methoxide (0.1 mole) was refluxed with stirring for 30 minutes. The mixture was naturalized with acetic acid and evaporated to dryness to obtain free nucleoside analogues.

FTIR and physical properties of compounds [11-13] were mentioned in Table (4).

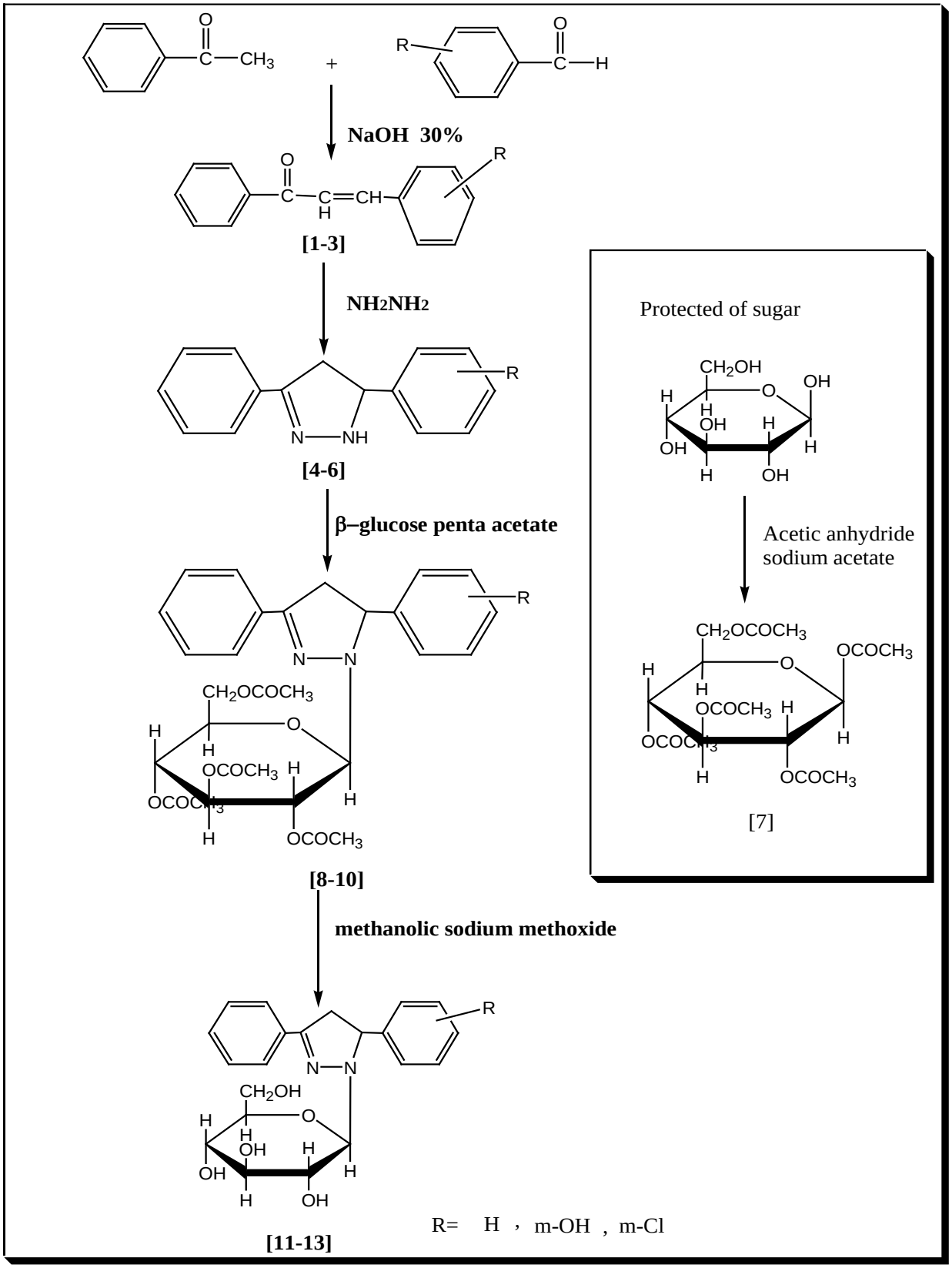
3.RESULT AND DISCUSSION

The new derivatives of nucleoside analogues were synthesized by the reaction sequences outlined in sheme (1).

Compounds [1-3] (chalcones) were formed from the reaction of acetophenone and benzaldehyde derivatives .FT-IR spectrum of compounds [1-3] observed the following bands (in Cm^{-1}) : (1661) C=O , (1565-1578) CH=CH , (1607) C=C aromatic , (3062) C-H aromatic .

Compound [5] observed band at 3450 Cm^{-1} belong to O-H group and compound [6] observed band at 774 Cm^{-1} attributed to C-Cl Table (1).

Compounds [4-6] were formed from the reaction of chalcone and hydrazine hydrate in the presence of ethanol absolute. FT-IR spectrum of compounds [4-6] observed the following bands (in Cm^{-1}) :(3385-3395) N-H, (1573-1590) C=C aromatic, (1638)C=N, (3030-3062) C-H aromatic .Compound [5] observed band at 3417 Cm^{-1} belong to O-H group and compound [6] observed band at 755 Cm^{-1} attributed to C-Cl . Table (2).



Scheme (1): formation of compounds [1-13]

After that β-glucose was protected by using sodium acetate anhydrous in the presence of acetic anhydride. The FTIR spectrum of this compound mentioned the following data in Cm^{-1} :
(1680) C=O, (2860-2900) C-H aliphatic Table(3).

Protected nucleoside analogues [8-10] were formed from the reaction of pyrazoline and β-glucose penta acetate. FT-IR spectrum of compounds [8-10] observed the following data (in Cm^{-1}) : (1681-1746) C=O , (1557-1561) C=C aromatic, (1600-1642) C=N, (3062) C-H aromatic table (3) . Compound [9] observed band at 3416 Cm^{-1} belong to the O-H group and

compound [10] observed band at 751 Cm^{-1} attributed to C-Cl T able (3).

Finally, these protected nucleoside analogues were allowed to hydrolized by methanolic sodium methoxide at reflux conditions. FT-IR spectrum of compounds [11-13] observed the following data (in Cm^{-1}) : (3443-3467) O-H , (1557-1596) C=C aromatic, (1635-1642) C=N, (3050-3062) C-H aromatic Table (4) . Compound [13] observed band at 759 Cm^{-1} attributed to C-Cl Table (4).

^{1}H-NMR(ppm) of compound [8]: at (7-8.1) aromatic protons, (3.9) CH pyrazoline ring , (1.9) CH_2 pyrazoline ring, (4.9-5.9) C-H sugar ring , (2) CH_3 group in sugar ring , (4.5) ppm CH_2 in sugar ring table (5). While the ^{13}C-NMR (ppm) of compound [8] : (122-138) aromatic carbons , (45) CH-C pyrazoline ring , (41)CH_2-C pyrazoline ring, (69-71) CH-C sugar ring, (20-21) CH_3-C group in sugar ring , (91.2) CH_2-C in sugar ring, (170) C=O, (149) C=N Table (6).

^{1}H-NMR (ppm) of compound [10] : (7.1-7.9) aromatic protons, (4) CH pyrazoline ring , (1.9) CH_2 pyrazoline ring, (4.9-5.9) C-H sugar ring , (2)CH group in sugar ring , (4.2) CH_2 in sugar ring table (5).While the ^{13}C-NMR (ppm) of compound [10]: (125-137) aromatic carbons ,(44) CH-C pyrazoline ring , (40) CH_2-C pyrazoline ring, (69-71) CH-C sugar ring, 20-21 CH_3-C group in sugar ring , (91.3) CH_2-C in sugar ring , (170) C=O , (129) C-Cl , (147) C=N Table (6).

^{1}H-NMR (ppm) of compound [12] : (7.1-8) aromatic protons , (3.8) CH pyrazoline ring , (1.8) CH_2 pyrazoline ring, (3.4-3.4) C-H sugar ring , (3.6) CH_2 in sugar ring ,(8.5) O-H table (5). ^{13}C-NMR (ppm) of compound [12] : (115-133) aromatic carbons , (45) CH-C pyrazoline ring , (40.5) CH_2-C pyrazoline ring, (69-77) CH-C sugar ring , (61) CH_2-C in sugar ring, (158) C=N Table (6).

^{1}H-NMR (ppm) of compound [13] : (7.2-7.5) aromatic protons , (3.8) CH pyrazoline ring , (1.7) CH_2 pyrazoline ring, (3.4) C-H sugar ring , (3.5) CH_2 in sugar ring table (5). ^{13}C-NMR (ppm) of compound [13] : (115-133) ppm aromatic carbons , (44) CH-C pyrazoline ring, (40) CH_2-C pyrazoline ring, (67-77) CH-C sugar ring , (63) CH_2-C in sugar ring , (147) C=N, (129) C-Cl Table (6).

Table (1): Physical properties and FT-IR spectral data of chalcones [**1-3**]

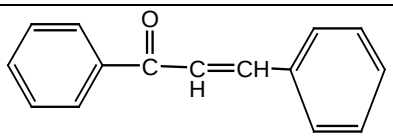
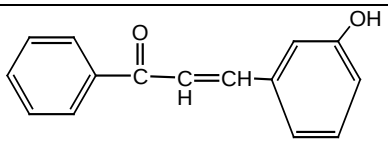
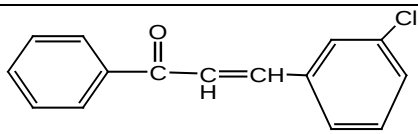
Compd. No.	Compound structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions Cm^{-1}				
					C=O	CH=CH	C=C Aromatic	C-H aromatic	others
1		58-60	50	Yellow	1661	1578	1607	3062	----
2		84-86	69	Orange	1661	1570	1607	3062	O-H 3450
3		48-50	73	Orange	1661	1565	1607	3062	C-Cl 774

Table (2): Physical properties and FT-IR spectral data of pyrazolines [**4-6]**

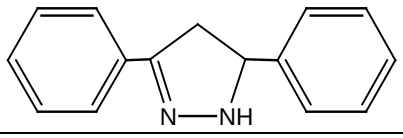
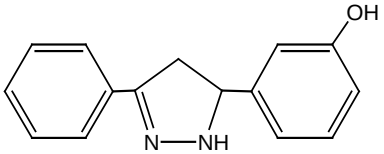
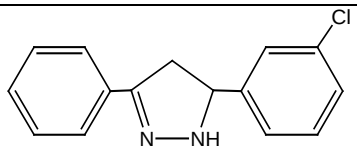
Compd. No.	Compound structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions Cm^{-1}				
					N-H	C=C aromatic	C=N	C-H aromatic	others
4		180-182	55	Brown	3390	1590	1638	3062	----
5		70-72	64	Yellow	3385	1590	1638	3062	O-H 3467
6		108-110	68	Brown	3395	1573	1638	3030	C-Cl 755

Table (3): Physical properties and FT-IR spectral data of compounds[**7-10**]

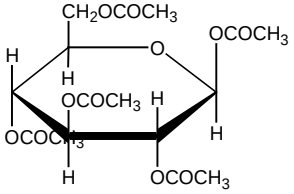
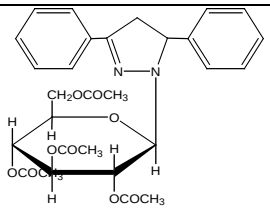
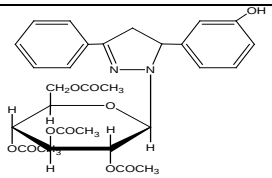
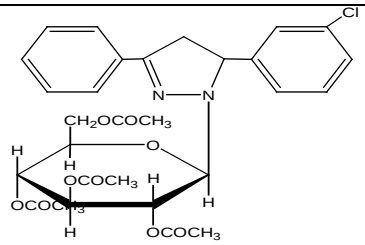
Compd. No.	Compound structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions Cm^{-1}				
					C=O	C=C aromatic	C=N	C-H aromatic	others
7		**130-132**	**85**	**White**	**1680**	**----**	**-----**	**----**	**C-H Aliphatic 2900-2860**
8		**60-62**	**75**	**Yellow**	**1681**	**1557**	**1638**	**3062**	**---**
9		78-80	57	Yellow	1746	1557	1642	3062	O-H 3416
10		84-86	40	Brown	1681	1561	1600	3062	C-Cl 751

Table (4): Physical properties and FT-IR spectral data of free nucleoside analogues [**11-13**]

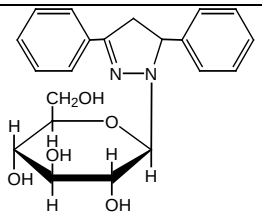
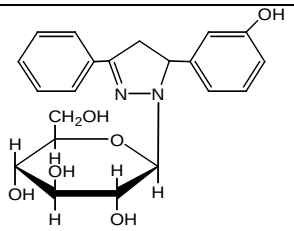
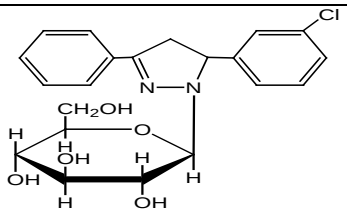
Compd. No.	Compound structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions Cm^{-1}				
					O-H	C=C aromatic	C=N	C-H aromatic	others
11		**syrup**	**70**	**Yellow**	**3467**	**1596**	**1635**	**3062**	**---**
12		**55-57**	**54**	**Brown**	**3459**	**1557**	**1642**	**3050**	**----**
13		**65-67**	**77**	**Brown**	3443	1557	1642	3055	C-Cl 759

Table (5): 1H-NMR-spectrum data of compounds [8,10,11 and 13]

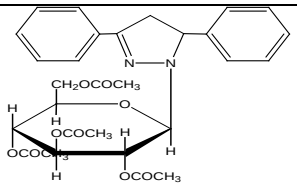
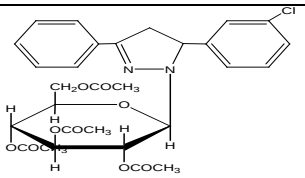
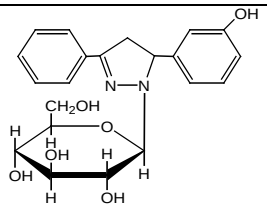
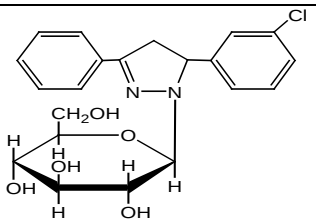
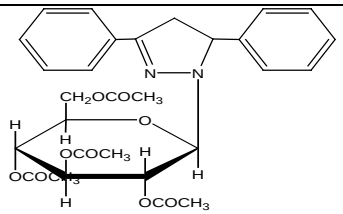
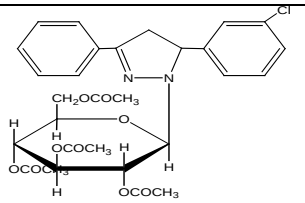
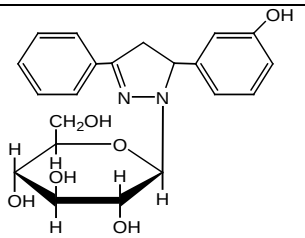
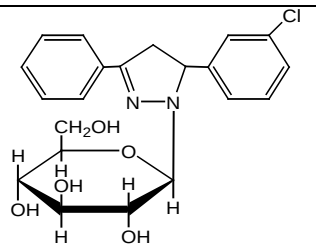
Compound No.	Compound structure	H-NMR spectral data δ ppm
8		7-8.1 (10H) aromatic protons, 3.9 (CH pyrazoline ring), 1.9(CH_2) pyrazoline ring, 4.9-5.9(C-H sugar ring), 2(CH_3 group in sugar ring), 4.5 (CH_2 in sugar ring)
10		7.1-7.9 (10H) aromatic protons,4 (CH pyrazoline ring), 1.9(CH_2) pyrazoline ring, 4.9-5.9 (C-H sugar ring), 2(CH_3 group in sugar ring), 4.2 (CH2 in sugar ring)
12		7.1-8 (10H) aromatic protons, 3.8 (CH pyrazoline ring), 1.8(CH_2) pyrazoline ring, 3.3-3.4 (C-H sugar ring)3.6 (CH_2 in sugar ring), 8.5 (O-H)
13		7.2-7.5(10H) aromatic protons, 3.8 (CH pyrazoline ring), 1.7(CH_2) pyrazoline ring, 3.4 (C-H sugar ring)3.5 (CH_2 in sugar ring)

Table (6): ^{13}C-NMR-spectral data of compounds [8,10,11 and 13]

Compound No.	Compound structure	^{13}C-NMR spectral data δ ppm
8		122-138 aromatic carbons , 45 (CH-C) pyrazoline ring), 41(CH_2-C) pyrazoline ring, 69-71 (CH-C sugar ring), 20-21(CH_3-C group in sugar ring), 91.2 (CH_2-C in sugar ring), 170 (C=O) , 149 (C=N)
10		125-137 aromatic carbons , 44 (CH-C) pyrazoline ring), 40(CH_2-C) pyrazoline ring, 69-71 (CH-C sugar ring), 20-21(CH_3-C group in sugar ring), 91.3 (CH2-C in sugar ring), 170 (C=O), 129 (C-Cl), 147 (C=N)
12		115-133 aromatic carbons , 45 (CH-C) pyrazoline ring), 40.5 (CH_2-C) pyrazoline ring, 69-77 (CH-C sugar ring), 61 (CH_2-C in sugar ring) , 158 (C=N)
13		115-133 aromatic carbons , 44 (CH-C) pyrazoline ring), 40(CH_2-C) pyrazoline ring, 67-77 (CH-C sugar ring), 63 (CH_2-C in sugar ring) , 147 (C=N), 129 (C-Cl)

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